

Quality of life as a therapeutic objective in the management of hepatic encephalopathy and the potential role of rifaximin- α

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Objective Quality of life (QoL) is impaired in patients with hepatic encephalopathy and rifaximin- α can improve QoL within 6 months. This study assessed the importance of QoL as a therapeutic objective in hepatic encephalopathy management; whether QoL is routinely assessed in hepatic encephalopathy patients in clinical practice and the role of rifaximin- α in this context.

Methods A survey was conducted of healthcare professionals (HCPs) from Europe and Australia involved in hepatic encephalopathy management. HCPs rated the importance of a range of therapeutic objectives on a 1–7 Likert scale (1 = not at all important; 7 = extremely important). HCPs were also required to provide three patient record forms (PRFs) based on their last three hepatic encephalopathy patients.

Results There were 218 HCP respondents, who provided 654 PRFs (patients treated with rifaximin- α , $n=347$; patients not treated with rifaximin- α , $n=307$). The mean Likert score was highest for the therapeutic objective 'improving a patient's QoL' (6.4), which was rated significantly more highly than all other therapeutic objectives, including 'reducing the patient's likelihood of hospital readmission' (6.1; $P<0.001$) and 'preventing death of the patient' (6.1; $P<0.001$). Despite this, only 28.3% of PRFs documented specific QoL data assessment. Patients receiving rifaximin- α were treated later in their disease course than those not receiving rifaximin- α .

Conclusions HCPs consider QoL improvement the main therapeutic objective in hepatic encephalopathy management, but most do not explicitly assess QoL. Earlier introduction of rifaximin- α may safeguard QoL improvement even when QoL monitoring is not possible. *Eur J Gastroenterol Hepatol* 33: e1032–e1038
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Introduction

Hepatic encephalopathy is a brain dysfunction caused by either liver insufficiency or portosystemic shunting or both, which manifests as a wide spectrum of neurologic or psychiatric abnormalities, ranging from subclinical alterations to coma [1]. Although the aetiology of hepatic encephalopathy has not been conclusively established, its pathophysiology is thought to involve elevated blood levels of gut-derived neurotoxins (particularly ammonia) entering the brain, due to the inability of the damaged liver to remove them from the blood circulation [2,3].

Systemic inflammation, neuroinflammation and endotoxaemia are also thought to be implicated [4]. Hepatic encephalopathy is one of the most debilitating complications of liver disease [1] and is associated with increased mortality [3,5]. Hepatic encephalopathy negatively affects patients' quality of life (QoL), both physically and mentally [6], resulting in a substantial burden on the lives of both patients and caregivers [1,7]. The economic burden of hepatic encephalopathy is also profound [8,9].

Hepatic encephalopathy guidelines recommend both the active treatment of overt hepatic encephalopathy and secondary prophylaxis to prevent hepatic encephalopathy recurrence [1]. Lactulose is recommended as the first choice for acute treatment and for the prevention of recurrence [1]. Rifaximin is recommended as adjunctive therapy to lactulose for the prevention of overt hepatic encephalopathy recurrence after the second episode [1]. The guidelines also recommend that prophylactic therapy be continued, unless precipitating factors (e.g. variceal bleeding, infections) have been well controlled, or liver function or nutritional status have improved [1].

Rifaximin- α is a locally acting oral antibiotic that is minimally absorbed in the gut to reduce the effects of intestinal flora, including ammonia-producing species [10–12]. It has also been shown to reduce the production of pro-inflammatory cytokines and endotoxin [4]. Rifaximin- α is indicated in Europe, Australia and New Zealand for the reduction in recurrence of episodes of overt hepatic encephalopathy in patients aged ≥ 18 years

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[13–15]. Evidence has demonstrated that the addition of rifaximin- α to standard lactulose therapy significantly reduces overt hepatic encephalopathy recurrence and hepatic encephalopathy-related hospitalisation, which may result in substantial reductions in healthcare resource utilisation over the long term [16–18]. Rifaximin- α has also been shown to significantly improve health-related QoL in patients with cirrhosis and recurrent hepatic encephalopathy [19].

Given the impact of hepatic encephalopathy on QoL, we conducted a survey of hepatic encephalopathy specialists in Europe and Australia to better understand how QoL is valued as an outcome measure in hepatic encephalopathy, whether QoL is routinely assessed in hepatic encephalopathy patients in clinical practice, and the role of rifaximin- α in this context.

Methods

Study design

Between September and December 2019, healthcare professionals (HCPs) from Australia, Belgium, Germany, Sweden, the Netherlands and the UK, with overall responsibility for the management of patients with hepatic encephalopathy, completed an online survey. These HCPs comprised hepatologists, gastroenterologists with special interest in hepatology and specialist liver nurses (UK only). In Germany, specialists included those who were hospital-based and office-based.

Screening criteria

To be included in the survey, HCPs were required to manage (i.e. diagnose, treat and discharge) patients with hepatic encephalopathy, and to be the main HCP for the long-term management of patients with hepatic encephalopathy at their institution. HCPs must personally have seen and treated at least 10 patients for hepatic encephalopathy (at least five patients in Belgium, Sweden, the Netherlands and Australia) in the last 3 months. HCPs were also required to have completed three patient record forms (PRFs) based on their last three patients with hepatic encephalopathy.

All patients recorded in PRFs were required to be aged between 18 and 75 years. PRFs of deceased patients or patients who were taking part in a clinical trial were excluded.

Outcomes

During the online survey, HCPs were asked the following questions: (1) ‘How important are each of the following therapy objectives to you for patients receiving hepatic encephalopathy primary or secondary prophylaxis therapy?’ and (2) ‘To what extent are each of the following factors important to you when deciding what therapies to prescribe to your patients for the prevention of further episodes of hepatic encephalopathy?’. The therapeutic objectives included in question 1 are outlined in Fig. 1a and the attributes included in question 2 are outlined in Fig. 1b. Responses were collected on a 1–7 Likert scale, where 1 corresponded to ‘not at all important’ and 7 corresponded to ‘extremely important’.

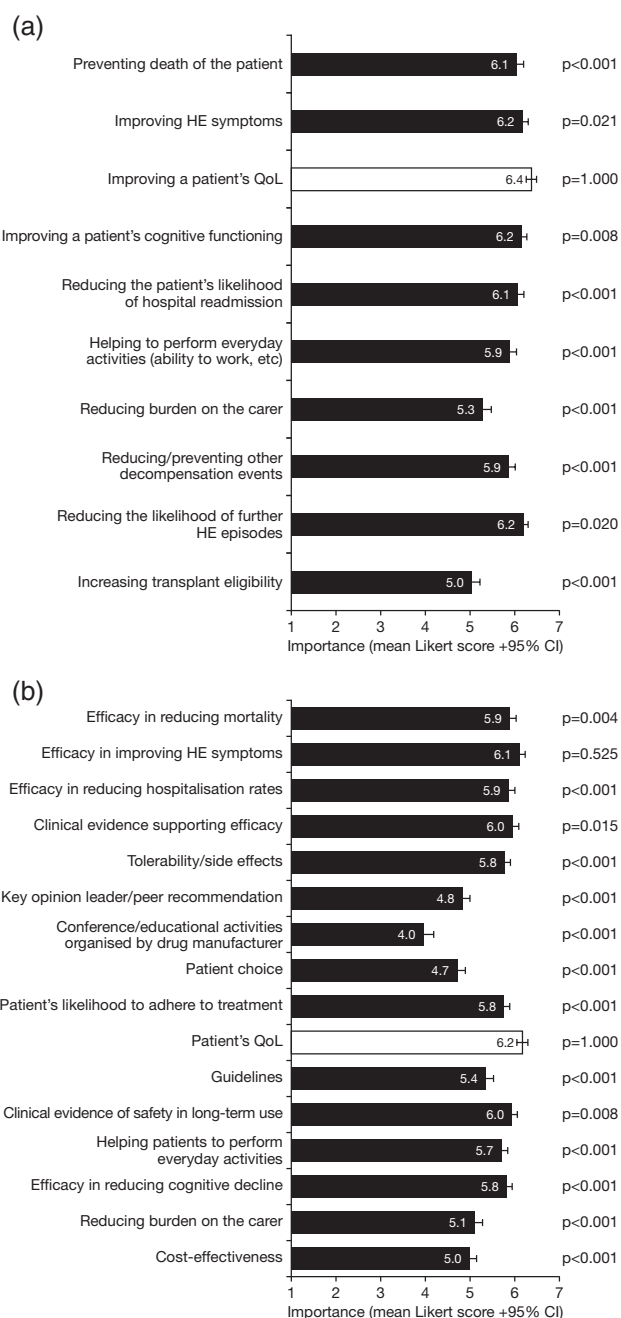


Fig. 1. Mean (95% confidence interval) Likert scores for the survey questions (a) ‘How important are each of the following therapy objectives to you for patients receiving HE primary or secondary prophylaxis therapy?’ and (b) ‘To what extent are each of the following factors important to you when deciding what therapies to prescribe to your patients for the prevention of further episodes of HE?’. Likert scale is 1–7, where 1 corresponds to ‘not at all important’ and 7 corresponds to ‘extremely important’. *P* values relate to two-sided tests comparing the mean score for QoL vs. each of the other therapeutic objectives/attributes. CI, confidence interval; HE, hepatic encephalopathy; QoL, quality of life.

PRFs were assessed to determine a range of demographic, clinical and therapy-related information (Table 1). This included the documentation of information relating to QoL.

Statistical methods

All analyses were carried out using the statistical package R version 4.0.2 (The R Foundation for Statistical

Table 1. Summary of information documented in patient record forms

	All patients	Patients who received rifaximin- α	Patients who did not receive rifaximin- α	<i>P</i> value ^a
Number of PRFs, <i>N</i>	654	347	307	
Country, <i>n</i> (%)				
Australia	93 (14.2)	68 (19.6)	25 (8.1)	<0.001
Belgium	60 (9.2)	27 (7.8)	33 (10.7)	0.19
Germany	231 (35.3)	92 (26.5)	139 (45.3)	<0.001
Netherlands	60 (9.2)	35 (10.1)	25 (8.1)	0.391
Sweden	60 (9.2)	42 (12.1)	18 (5.9)	0.006
UK	150 (22.9)	83 (23.9)	67 (21.8)	0.525
Age, mean (95% CI)	57.5 (56.7–58.3) ^b	58.4 (57.2–59.5) ^c	56.6 (55.4–57.8) ^d	0.033
Male sex, <i>n</i> (%)	451 (69.4) ^e	245 (71.0) ^f	206 (67.5) ^g	0.338
What was the precipitating factor for the patient's last hepatic encephalopathy event? <i>n</i> (%)				
Electrolyte or metabolic disturbance	181 (27.7)	101 (29.1)	80 (26.1)	0.385
Drugs and medications	73 (11.2)	40 (11.5)	33 (10.7)	0.753
Infection	196 (30.0)	111 (32.0)	85 (27.7)	0.231
Constipation	124 (19.0)	65 (18.7)	59 (19.2)	0.874
Renal failure	50 (7.6)	26 (7.5)	24 (7.8)	0.876
Variceal bleeding	136 (20.8)	69 (19.9)	67 (21.8)	0.543
Ascites	139 (21.3)	78 (22.5)	61 (19.9)	0.417
Transjugular intrahepatic portosystemic shunt	36 (5.5)	22 (6.3)	14 (4.6)	0.32
Other	28 (4.3)	16 (4.6)	12 (3.9)	0.659
Unknown	51 (7.8)	21 (6.1)	30 (9.8)	0.077
Who referred the patient to you? <i>n</i> (%)				
Accident and emergency/emergency department/emergency room	288 (44.0)	163 (47.0)	125 (40.7)	0.108
Gastroenterology ward	149 (22.8)	86 (24.8)	63 (20.5)	0.195
Critical care	31 (4.7)	17 (4.9)	14 (4.7)	0.839
Cardiology	10 (1.5)	2 (0.6)	8 (2.6)	0.035
Nephrology	7 (1.1)	2 (0.6)	5 (1.6)	0.192
Neurology	3 (0.5)	0	3 (1.0)	0.065
Occupational therapy	1 (0.2)	1 (0.3)	0	0.347
Rheumatology	1 (0.2)	0	1 (0.3)	0.288
General medicine	60 (9.2)	29 (8.4)	31 (10.1)	0.442
Primary care (general practitioner/primary care provider)	83 (12.7)	42 (12.1)	41 (13.4)	0.632
Geriatrics/care of the elderly	3 (0.5)	3 (0.9)	0	0.103
Psychiatry or addiction services	4 (0.6)	1 (0.3)	3 (1.0)	0.26
Office-based specialist (e.g. gastroenterologist)	5 (0.8)	2 (0.6)	3 (1.0)	0.558
Other	6 (0.9)	4 (1.2)	2 (0.7)	0.503
Patient not referred	49 (7.5)	14 (4.0)	35 (11.4)	<0.001
What was the patient referred to you with?				
Hepatic encephalopathy	396 (60.6)	229 (66.0)	167 (54.4)	0.002
Liver disease/cirrhosis of the liver	445 (68.0)	253 (72.9)	192 (62.5)	0.004
Infection	154 (23.5)	89 (25.6)	65 (21.2)	0.179
Constipation	76 (11.6)	42 (12.1)	34 (11.1)	0.683
Renal failure	65 (9.9)	37 (10.7)	28 (9.1)	0.511
Variceal bleeding	116 (17.7)	55 (15.9)	61 (19.9)	0.18
Ascites	172 (26.3)	99 (28.5)	73 (23.8)	0.169
Dementia	17 (2.6)	8 (2.3)	9 (2.9)	0.616
Stroke	21 (3.2)	10 (2.9)	11 (3.6)	0.612
Aphasia	6 (0.9)	3 (0.9)	3 (1.0)	0.88
Hepatitis	57 (8.7)	36 (10.4)	21 (6.8)	0.11
Other	13 (2.0)	6 (1.7)	7 (2.3)	0.615
What is the underlying cause of this patient's liver disease?				
Alcoholism	440 (67.3)	220 (63.4)	220 (71.7)	0.025
Hepatitis B	56 (8.6)	27 (7.8)	29 (9.4)	0.448
Hepatitis C	95 (14.5)	55 (15.9)	40 (13.0)	0.308
Nonalcoholic fatty liver/nonalcoholic steatohepatitis	103 (15.7)	63 (18.2)	40 (13.0)	0.073
Acute liver failure (due to drug overdose)	15 (2.3)	11 (3.2)	4 (1.3)	0.112
Acute liver failure (other cause)	20 (3.1)	12 (3.5)	8 (2.6)	0.528
Autoimmune hepatitis	23 (3.5)	11 (3.2)	12 (3.9)	0.609
Autoimmune primary biliary cirrhosis	15 (2.3)	10 (2.9)	5 (1.6)	0.286
Autoimmune primary sclerosing cholangitis	6 (0.9)	5 (1.4)	1 (0.3)	0.136
Other	16 (2.4)	7 (2.0)	9 (2.9)	0.451
Number of hepatic encephalopathy episodes the patient has had in the last 12 months, mean (95% CI)	1.6 (1.4–1.7) ^h	1.7 (1.5–1.9) ⁱ	1.4 (1.2–1.6) ^j	0.032
Number of hepatic encephalopathy episodes the patient has had since diagnosis, mean (95% CI)	2.7 (2.5–2.9) ^k	3.1 (2.8–3.4) ^l	2.1 (1.9–2.3) ^m	<0.001
Which of the following comorbidities has the patient suffered from in the last 12 months? <i>n</i> (%)				
Spontaneous bacterial peritonitis	164 (25.1)	105 (30.3)	59 (19.2)	0.001
Renal failure	134 (20.5)	93 (26.8)	41 (13.4)	<0.001
Variceal bleeding	167 (25.5)	96 (27.7)	71 (23.1)	0.185
Diabetes	129 (19.7)	73 (21.0)	56 (18.2)	0.371
Obesity	150 (22.9)	82 (23.6)	68 (22.1)	0.654
Cardiovascular disease	99 (15.1)	45 (13.0)	54 (17.6)	0.1
Inflammatory bowel disease	35 (5.4)	15 (4.3)	20 (6.5)	0.214

(continued)

Table 1. (continued)

	All patients	Patients who received rifaximin- α	Patients who did not receive rifaximin- α	P value ^a
Connective tissue disease	3 (0.5)	2 (0.6)	1 (0.3)	0.637
Substance abuse (incl. alcohol and recreational drugs)	177 (27.1)	84 (24.2)	93 (30.3)	0.081
Other	32 (4.9)	18 (5.2)	14 (4.6)	0.711
None	96 (14.7)	47 (13.5)	49 (16.0)	0.384
Is the patient currently receiving therapy for hepatic encephalopathy prophylaxis? (Yes), <i>n</i> (%)	553 (84.6)	327 (94.2)	226 (73.6)	<0.001
What is/are the current/most recent therapy/therapies the patient has received to reduce hepatic encephalopathy occurrence? <i>n</i> (%)				
Lactulose	540 (82.6)	277 (79.8)	263 (85.7)	0.05
Neomycin (UK: Nivemycin)	28 (4.3)	10 (2.9)	18 (5.9)	0.06
Rifaximin- α	347 (53.1)	347 (100)	0	1.000
Metronidazole (UK: Flagyl)	38 (5.8)	15 (4.3)	23 (7.5)	0.084
Probiotics	67 (10.2)	26 (7.5)	41 (13.4)	0.014
Saline enema	30 (4.6)	15 (4.3)	15 (4.9)	0.732
Other antibiotics	15 (2.3)	6 (1.7)	9 (2.9)	0.306
Other treatments	13 (2.0)	9 (2.6)	4 (1.3)	0.239
None	27 (4.1)	0	27 (8.8)	<0.001
Was a GP referral letter given to the patient when he or she was discharged from hospital? <i>n</i> (%)	544 (83.2)	294 (84.7)	250 (81.4)	0.262
Did you collect any QoL data for this patient?	185 (28.3)	86 (24.8)	99 (32.2)	0.034
L-ornithine-l-aspartate (Hepa-Merz) use (yes), <i>n</i> (%)	77 (11.8)	29 (8.4)	48 (15.6)	0.004
Duration since first diagnosis of hepatic encephalopathy, mean (95% CI) years	2.9 (2.6–3.2) ⁿ	2.9 (2.5–3.2) ^o	3.0 (2.6–3.4) ^p	0.696

CI, confidence interval; PRF, patient record form; QoL, quality of life.

^aP values for two sample *t*-tests comparing patients who received rifaximin- α vs. those who did not receive rifaximin- α .

^b*N* = 634.

^c*N* = 331.

^d*N* = 303.

^e*N* = 650.

^f*N* = 345.

^g*N* = 305.

^h*N* = 463.

ⁱ*N* = 273.

^j*N* = 190.

^k*N* = 427.

^l*N* = 254.

^m*N* = 173.

ⁿ*N* = 625.

^o*N* = 324.

^p*N* = 301.

Computing, 2020). Mean [95% confidence interval (CI)] Likert scores were calculated for the two survey questions. Two-sided *t*-tests were conducted to compare (1) the mean score for the therapeutic objective ‘improving a patient’s QoL’ with the mean scores for each of the other therapeutic objectives (question 1) and (2) the mean score for the attribute ‘patient’s QoL’ with the mean scores for each of the other attributes (question 2). Data from PRFs were assessed for the total patient population and for the subgroups of patients who received rifaximin- α (in any combination with other treatments) and those who did not receive rifaximin- α . Two sample *t*-tests were conducted to compare PRF characteristics between the subgroups of patients who were vs. were not treated with rifaximin- α .

Ethics

This survey study was conducted by Ipsos Healthcare, an independent market research agency based in Germany, on behalf of Norgine Ltd. The methodology complied with German Market Research Guidelines, European Society for Opinion and Market Research e.V. guidelines, the Working Group of German Market and Social Research (ADM) guidelines, and European Pharmaceutical Market Research Association (EphMRA) guidelines. As per EphMRA code of conduct 2019, section 1.3, this study complied with the European Federation of Pharmaceutical Industries and Associations requirements for market research (as opposed

to clinical research), and thus did not require clinical research ethics committee approval. The study complied with all German data protection regulations. Participation in the online survey was voluntary. All patient data included in the PRFs were anonymised prior to assessment.

Results

Study sample

A total of 2996 HCPs were initially approached, from whom there were 218 respondents (Australia, *n* = 31; Belgium, *n* = 20; Germany, *n* = 77; Netherlands, *n* = 20; Sweden, *n* = 20 and UK, *n* = 50). HCPs provided a total of 654 PRFs (Australia, *n* = 93; Belgium, *n* = 60; Germany, *n* = 231; Netherlands, *n* = 60; Sweden, *n* = 60; UK, *n* = 150), comprising 347 patients treated with rifaximin- α and 307 patients not treated with rifaximin- α (Table 1).

Online survey

In answer to the question ‘How important are each of the following therapy objectives to you for patients receiving hepatic encephalopathy primary or secondary prophylaxis therapy?’, the mean Likert score was highest for ‘improving a patient’s quality of life’ (6.4) (Fig. 1a). The mean score for this therapeutic objective was significantly higher than the mean scores for all other therapeutic objectives, including ‘reducing the patients likelihood of hospital readmission’

(6.1; $P < 0.001$) and 'Preventing death of the patient' (6.1; $P < 0.001$). Mean scores for the therapeutic objective 'improving a patient's QoL' ranged from 6.3 in Germany, the Netherlands and UK to 6.8 in Australia (Fig. 2).

In answer to the question 'To what extent are each of the following factors important to you when deciding what therapies to prescribe to your patients for the prevention of further episodes of hepatic encephalopathy?', the mean Likert score was highest for 'improving a patient's QoL' (6.2) (Fig. 1b). The mean score for this attribute was significantly higher than the mean scores for all other attributes, with the exception of 'efficacy in improving hepatic encephalopathy symptoms' (6.1; $P = 0.525$).

Patient record forms

Information documented in the PRFs is summarised in Table 1. The majority of patients in the overall sample were male (69.4%) and had been referred to their HCPs for liver disease/cirrhosis of the liver (68.0%) and/or hepatic encephalopathy (60.6%). Patients had experienced a range of comorbidities (complications of cirrhosis and other medical conditions) in the previous 12 months, including substance abuse (27.1%), variceal bleeding (25.5%), spontaneous bacterial peritonitis (25.1%), obesity (22.9%) and renal failure (20.5%).

Despite the high importance HCPs placed on QoL improvement, the proportion of patients who had QoL data documented was significantly lower than the proportion of patients who did not have QoL data documented (28.3 vs. 71.7%; $P < 0.001$). The proportion of patients for whom QoL data were documented ranged from 2.2% in Australia to 51.7% in Belgium (Fig. 2).

Overall, while 84.6% (553/654) of patients were receiving some therapy for hepatic encephalopathy

prophylaxis, 88.0% (227/258) of patients treated for secondary hepatic encephalopathy prophylaxis were treated with rifaximin- α . Patients treated with rifaximin- α had experienced more hepatic encephalopathy episodes than those who did not receive rifaximin- α , both in the previous 12 months (mean 1.7 vs. 1.4; $P = 0.032$) and since hepatic encephalopathy diagnosis (3.1 vs. 2.1; $P < 0.001$). The proportions of patients with comorbidities commonly associated with hepatic encephalopathy was higher for patients receiving rifaximin- α vs. those not receiving rifaximin- α : significantly higher for spontaneous bacterial peritonitis (30.3 vs. 19.2%; $P = 0.001$) and numerically higher for variceal bleeding (27.7 vs. 23.1%; $p = 0.185$). The proportion of patients with renal failure was also significantly higher for patients receiving rifaximin- α vs. those not receiving rifaximin- α (26.8 vs. 13.4%; $P < 0.001$). The proportion of patients for whom QoL data were documented was significantly lower for those receiving rifaximin- α vs. those not receiving rifaximin- α (24.8 vs. 32.2%; $P = 0.034$).

Discussion

This study revealed important insights into the therapeutic objectives of HCPs directly involved in the management of patients with hepatic encephalopathy. QoL emerged as the most important therapeutic objective overall, with a mean score of 6.4 on a Likert scale of 1–7 (where 7 corresponded to 'extremely important'). Improving a patient's QoL was rated significantly more highly than any other therapeutic objective, including reducing the likelihood of hospital readmission and preventing the death of the patient. Similarly, when HCPs were asked about factors that are important to them when deciding what therapies to prescribe patients to prevent further episodes of hepatic

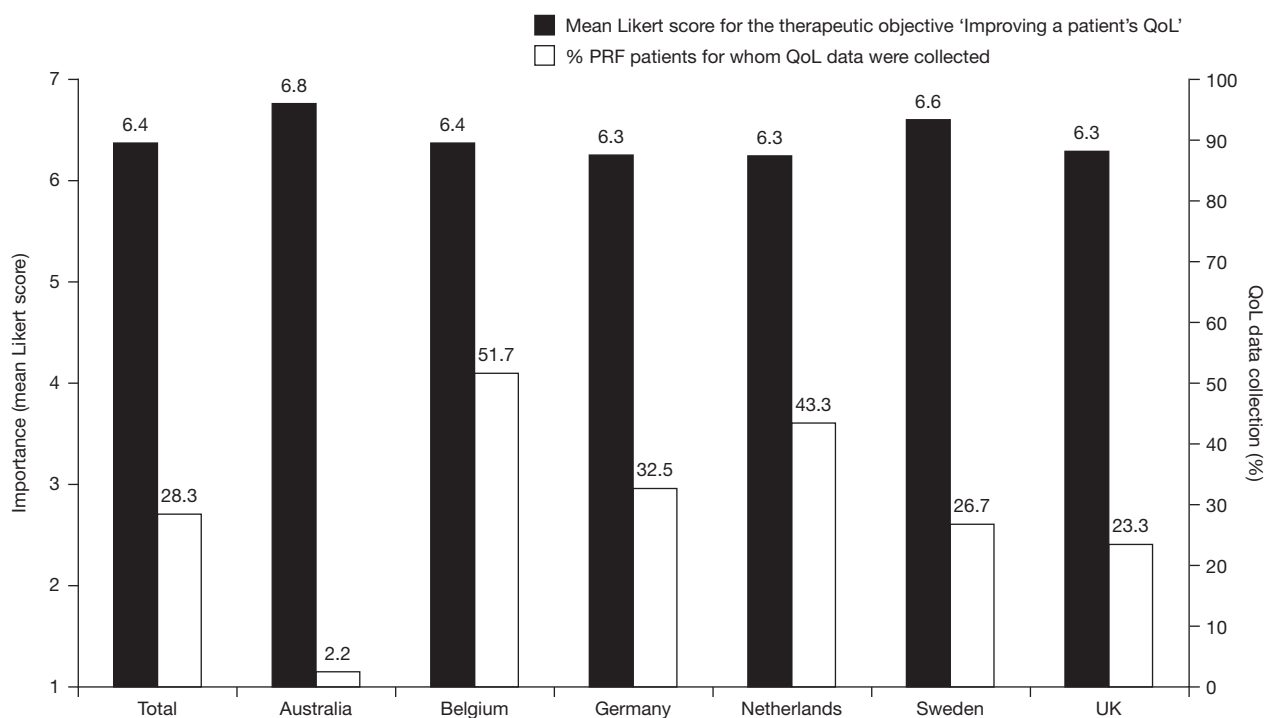


Fig. 2. Mean Likert scores for HCPs answering the survey question 'How important are each of the following therapy objectives to you for patients receiving HE primary or secondary prophylaxis therapy? Improving a patient's QoL' and percentages of PRF forms that documented QoL data, by country. HCP, healthcare professional; PRF, patient record form; QoL, quality of life.

encephalopathy, QoL was again the most highly rated attribute, with a mean score of 6.2. QoL was rated significantly more highly than all the other attributes, with the exception of 'efficacy in improving hepatic encephalopathy symptoms', for which the mean score was still lower than that for QoL (6.1) but not significantly so.

There was a marked mismatch in the perceived importance of QoL as a therapeutic objective in hepatic encephalopathy management and the documented formal assessment of QoL in clinical practice, as demonstrated by the finding that only 28.3% of PRFs included QoL data. This mismatch was more notable in some countries than others; for example, HCPs from Australia gave QoL the highest rating of importance of all the countries included (mean score, 6.8), but only 2.2% of PRFs from Australia documented QoL data. Reasons for this mismatch are unclear but might include insufficient time in the clinic to assess QoL correctly, and a lack of easy-to-use measures to assess QoL in patients with hepatic encephalopathy. Tests validated for use in covert hepatic encephalopathy may prove useful in this regard; for example, the Clinical Covert Hepatic Encephalopathy score has been developed and validated for use as an easy-to-perform measure for identifying patients with cirrhosis at risk of covert hepatic encephalopathy, which has been shown to correlate with QoL and the risk of first-time overt hepatic encephalopathy [20]. Similarly, the Sickness Impact Profile questionnaire for Covert Hepatic Encephalopathy score is based on QoL outcomes and has been developed and validated as a simple, patient-administered, diagnostic measure to identify patients at high risk of developing overt hepatic encephalopathy who might benefit from prophylactic therapy [21]. Another explanation for this unexpected low rate of formal assessment of QoL in clinical practice may be related to a lack of precision of the question related to this item. In clinical practice, we can assume that some indicators of QoL, such as sleep disturbances or inversion of the circadian rhythm, are often (if not always) assessed when a patient with hepatic encephalopathy is seen. Overall, these data indicate that easy-to-use tools to assess QoL would be of interest and could help patient management.

The study also revealed further insights into the use of rifaximin- α . Among the 88.0% of patients who were treated for secondary hepatic encephalopathy prophylaxis with rifaximin- α , the vast majority 84.1% (191/227) also received lactulose, indicating a high acceptance of the concept of adding rifaximin- α to lactulose in this setting. This percentage is considerably higher than previous reports; for example, a retrospective analysis of a nationally representative US commercial claims database found that only 27.4% of patients with hepatic encephalopathy were prescribed rifaximin- α after being seen by gastroenterologist/hepatologist and advanced practice provider [22]. Similarly, an analysis of prescription patterns of general practitioners in Germany found that only 22.5% of patients were prescribed rifaximin- α after an episode of hepatic encephalopathy (Labenz, personal communication of unpublished data). Reasons for this discrepancy are unclear, but might indicate a level of recall bias in the current study. Patients who received rifaximin- α had experienced more hepatic encephalopathy episodes (in the previous 12 months and since hepatic encephalopathy

diagnosis) than those who did not receive rifaximin- α . Patients treated with rifaximin- α also reported higher levels of comorbidities, such as spontaneous bacterial peritonitis, variceal bleeding and renal failure, than those not treated with rifaximin- α . These findings confirm that rifaximin- α is used relatively late in a patient's disease course, most likely when lactulose alone is providing inadequate efficacy and/or the patient's condition has worsened. Other potential reasons for the relatively late use of rifaximin- α may include local/national limitations and restrictions in the criteria for using rifaximin- α and institutional limitations in funding for rifaximin- α ; although evidence has shown that the addition of rifaximin- α to lactulose therapy results in substantial reductions in healthcare resource utilisation over the long term [16–18].

Evidence demonstrates that patients treated with rifaximin- α relatively early in their disease course (during the first 6 months) experience improvements in QoL [19,23,24]. For example, a subanalysis of the pivotal rifaximin- α Phase 3 trial demonstrated that rifaximin- α significantly improved health-related QoL [assessed using the Chronic Liver Disease Questionnaire (CLDQ)] over 6 months in patients with cirrhosis who had experienced at least two overt hepatic encephalopathy episodes within the previous 6 months [19]. Statistically significant and clinically important improvements in health-related QoL measures were observed with rifaximin- α vs. placebo across each of the six CLDQ domains (fatigue, abdominal symptoms, systemic symptoms, activity, emotional function and worry) and for the overall CLDQ score (all $P < 0.0001$) [19]. Other evidence has shown that treatment of minimal hepatic encephalopathy with lactulose, probiotics or L-ornithine L-aspartate can improve health-related QoL [25–27], further supporting early intervention to improve QoL outcomes.

A limitation of this study was that QoL monitoring was assessed by examining the documentation of QoL information in PRFs, which may have underestimated the overall assessment of QoL by HCPs, because the content of conversations resulting from general enquiries that might have encompassed aspects of QoL, such as 'How are you feeling?', may not have been captured in PRFs. In addition, the reported high use of rifaximin- α for secondary hepatic encephalopathy prophylaxis, in comparison with other studies, may indicate a level of recall bias in the current study, as previously mentioned.

In conclusion, the findings from this study demonstrate that improvement in QoL is a top-rated outcome in hepatic encephalopathy management. However, it seemed to be rarely assessed in this study performed in European and Australian patients with hepatic encephalopathy. The earlier introduction of rifaximin- α may safeguard QoL improvement even when QoL monitoring is not easy to assess. Easy-to-use tools are needed to assess QoL in clinical practice in patients with hepatic encephalopathy.

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Conflicts of interest

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